Remarks

Upon entry of the above amendments, this application will contain claims 1, 2, 5, 6, 8, 16, 19, 21-23, and 33-41. In the latest Office Action dated 2 November 2009, the restriction requirement was withdrawn. Claims 21-23, 26 and 39-41 have been rejoined for examination. In this Submission, claim 26 has been canceled. No other claims have been amended, added or canceled. In light of the above amendments and the following comments it is believed that this application in condition for allowance. Prompt reconsideration leading to the allowance of all pending claims is requested.

I. Interview Summary

The undersigned attorney thanks Examiner Puttlitz for the examiner initiated interview of 23 October 2009. The interview summary provided by the Examiner dated 2 November fairly characterized the substance of the discussion.

II. Allowed Claims

Claims 1, 2, 5, 6, 8, 16, 19, and 33-38 were deemed allowable.

III. Rejections Under 35 §§102 and 103

Withdrawal of all prior rejections under §102 and §103 are acknowledged.

IV. Restriction Requirement

Withdrawal of the Election/Restriction Requirement set forth in the office action dated 10 December 2008 is acknowledged for method claims 21-23, 26, 39-41.

V. Rejections under 35 USC §112, 1st paragraph

Claims 21-23, 26, and 39-41 were rejected under 35 USC 12, 1st paragraph. It was stated in the Office Action that while the specification was enabling for the those methods or treating diseases or symptoms associated with stimulating the vitamin D receptor does not reasonably enable treating all symptoms or conditions associated with the recited diseases. (Office Action, page 3.) The applicants respectfully traverse this rejection.

As a preliminary matter the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason

> to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

In re Marzocchi, 439 F.2d 220, 222-223 (CCPA, 1971)(Emphasis added.) Only after the PTO provides *evidence* showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. In re Brana, 51 F. 3d 1560, 1566 (Fed. Cir. 1995.)

The instant Office Action is wholly deficient in meeting this burden. Nowhere in the Office Action is there any support or evidence that the one skilled in the art would *reasonably* doubt that the claims were enabled. (Office Action, page 6.) The Office Action does repeat, without analysis the bare and oft used allegation to the unpredictability of the chemical arts; then provides unsupported allegations that the statement is on its face contrary to generally accepted scientific principles; and pronounces that the state of the art does not support that all symptoms of the recited diseases can be treated-- *without* a cite to any specific reference or teaching,

The oft quoted passage from Marzocchi directed toward the unpredictability of the chemical arts fails consider the admonition from that same court that immediately follows.

> Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

In re Marzocchi, 439 F.2d 220, 223 (CCPA, 1971)(Emphasis added.) And in Brana, in which the applicants claimed compounds useful for the treatment of cancer, the court stated that:

> "[W]e do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. In re Jolles, 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng *et al.*, discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models."

In re Brana, 51 F.3d 1560 1566 (Fed. Cir. 1995)(Emphasis in original.)

The US PTO did not meet its burden. The Office Action did not provide any evidence or

acceptable reasoning to substantiate the alleged lack of enablement for the claimed invention.

The "Wands factors" are intended to provide a framework to analyze the enablement requirement. In re Wands, 858 F.2d 731 (Fed. Cir 1988). The analysis must consider all the evidence related to each of these factors, and any conclusions of non-enablement must be based on the evidence as a whole.

The rejection in the Office Action does not provide any evidence or analysis to support a *prima facie* basis for the rejections of the claims. Merely conjuring up the name "Wands" does not satisfy the analysis requirement. The instant Office Action provided only the briefest mention of the "Wands factors" but was lacking any cogent analysis. Other than a mere reference to the unpredictability of the chemical arts and a cursory mention to the prior art, no reasoned explanation for the rejection is provided.

The Office Action did state that the rejected claims cover treating *all symptoms* of the recited diseases with the instant compounds and therefore are not enabled. The Office Action continued along this line of reasoning by alleging that the Background section describes other known compounds that can only alleviate those *symptoms* associated with the stimulation of vitamin D receptors; and that the prior art does not indicate that the compounds can act by some other mechanism. (Office Action, p 4.)

Despite repeated references in the Office Action to treatments of all *symptoms* of the diseases, the claims are directed to treating specific diseases. Claims 21-23, and 39-41 and actually recite to a method of treating one or more of *diseases* i.e. osteoporosis, psoriasis, scleroderma, and/or seborrheic dermatitis using one or more of the claimed compounds. Claim 26 has been canceled.

Diseases and symptoms of the diseases are not the same. It is not necessary that a treatment for a specific symptom also treat the disease that causes the symptom and vice versa. For example, while it is known that the symptoms of a cold can be treated, the same treatments may not also treat the actual cold. In fact the symptoms of a cold, i.e., runny nose, water eyes, etc. are actually a result the body's natural defenses combating or "treating" the cold. In effect the "treatment" of the disease (or viral infection in this example) causes the symptoms.

It was also stated that the instant disclosure doesn't remedy the state of the art, *which by the way is not analyzed in the Office Action,* since the specification only describes compounds that allegedly work by stimulating vitamin D receptors. (Office Action, p 5. Referring to the Background section; italicized comment added.)

There is no requirement that the application enable the only therapeutic method or mechanism for treating the recited diseases. Nor is there a requirement that the application to

enable all the methods or mechanisms useful for treating the recited diseases.

The Background section actually states that 1α,25-dihydroxyvitamin D3[1] interacts with the nuclear hormone receptor, vitamin D receptor (*id.*, ¶0001), and that the activity of 1α,25-dihydroxyvitamin D3 suggests wide clinical applications (*id.*, ¶0002).[2] The Background section also specifically references two articles published in peer reviewed journals. The first article, Nagpal et al. "Vitamin D Analogues: Mechanism of Action of Therapeutic Applications" Curr. Med. Chem. 2001, 8, 1661-1679 (herein after "Nagpal") is co-authored by some of the inventors listed in the instant application. The second article is Boehm et al. "Novel Nonsecosteroidal Vitamin D Mimics Exert VDR-Modulating Activities With Less Calcium Mobilization Than 1α,25-Dihydroxyvitamin D_3", Chemistry and Biology 1999, 6(5) 265-275. (Hereinafter "Boehm". See the present application, ¶¶0004 and 0009.) Both articles have already been submitted to the Patent Office for consideration.[3]

These articles as noted and discussed more fully below, disclose that vitamin D receptor[4] is a ligand-dependent transcription factor which regulates gene expression and has been implicated in a number of cellular processes. Modification of VDR can be used to treat a variety of diseases including each of the four diseases, i.e., osteoporosis, psoriasis, scleroderma, and/or seborrheic dermatitis for which treatment is claimed. Further vitamin D receptor has also identified in a variety of cell lines and primary cells obtained from various tissues.

As asserted above while the office action is wholly deficient in meeting its burden by failing to fully consider the Wands factors and provide sufficient support for the rejection, never-the less, in order the advance the prosecution of this case, the following is a discussion of the Wands factors: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims

The Amount of Direction:

Prior art teaching on VDR modification: Nagpal states that "1α,25-dihydroxyvitamin D3 interacts with the vitamin D receptor (VDR)" and that "VDR has been identified in a variety of cell lines and primary cells obtained form [sic] various tissues". (Nagpal, p 1661, left column.) Further it is noted that "[a]t the molecular level, 1α,25-dihydroxyvitamin D3 and its synthetic

[1] 1α,25-dihydroxyvitamin D3 may also be referred to as 1α,25$(OH)_2$D3 or 1α,25$(OH)_2D_3$.
[2] Unless specifically noted to the contrary all citations to the present application refer to the published patent application publication no. US2006029335, published 28 December 2006.
[3] All references cited herein have been previously submitted to the US PTO.
[4] Vitamin D receptor may alternatively be referred to in the cited articles and in the instant Response as "VDR"

analogs exert their effect through a heterodimer of VDR and retinoid X receptor (RXR)". (Nagpal, p 1662, left column.) Nagpal lists a number of examples of regulation of gene expression by VDR ligands. This is indicative that modification of VDR with bound ligands can potentially affect different tissues and diseases.

The present application provides compounds, which have been evaluated for their binding efficiency to the VDR through the RXR-VDR hetereodimer assay. (Application, ¶0484.) Desired compounds exhibit an EC_{50} value of less than about 600 nM. The results of that assay are found in Table 3, ¶00832.) Clearly from the EC_{50} values in the Table 3 several representative compounds exhibit high VDR binding.

Examples of prior art teaching related to psoriasis:

Nagpal discloses some vitamin D3 mimics in a Table on page 1669. The vitamin D mimics or modulators mimic many of the activities of the 1α,25-$(OH)_2D_3$; including interacting with VDR, to stimulate transcription from a VDR response element in cotransfection assays in a VDR-dependent manner and inhibit among others primary keratinocytes. (Nagpal, page 1669, right column). Under the subtitle "THERAPEUTIC APPLICATIONS VDR in Psoriasis" it is stated that since psoriasis involves hyperperliferation of epidermal keratinocyes, it appeared logical that 1α,25-dihydroxyvitamin D3 could be exploited to treat this disease, and that this provides a reasonable basis for the clinical use of VDR ligands in psoriasis. (Nagpal, page 1670, left column.)

Boehm also states that the molecular mechanism of 1α,25$(OH)_2D_3$ is known to be through binding to its intracellular receptor, the vitamin D receptor (VDR), and that this binding results in heterodimer formation with retinoid X receptor (RXR), which enables high-affinity binding to vitamin D responsive element (VDRE) sequences within, and subsequent transcriptional activation of vitamin D target genes. (Boehm, page 265, left column.) Boehm also lists the some of the same VDR mimics as Nagpal does. These VDR mimics interact with VDR-dependent transcription activation, including inhibiting proliferation of primary human keratinocytes among others. (Boehm, page 226 and 269.) The VDR mimics also exert many of the actions of 1α,25$(OH)_2D_3$ "including inhibiting the growth of and induce morphological changes in human keratinocytes, which are predictive assays for the utility of compounds in the treatment of psoriasis". (Boehm, page 271, right column, bottom.)

The overwhelming conclusion from these peer reviewed articles is that VDR ligands including VDR mimics such as those presently claimed in the instant application bind to VDR and can be used to treat psoriasis.

The present application enables the treatment of psoriasis: The present application also describes assays for evaluating compounds for the treatment of psoriasis including the RXR-VDR heterodimer assay and the Keratinocyte Proliferation Assay (*id.*, ¶¶0847, 0853) and the IL-10 Assay (*id.*, ¶0853). Data for representative compounds of the present invention in the karetinocyte proliferation assay and the IL-10 assay can be found in Table 4. (*Id.*, 0833). Acceptable results for these assay is an EC_{50} value of less than about 300 nM and 200nM, respectively. Clearly many of the claimed compounds exhibit an EC_{50} value within the acceptable range in both the karetinocyte proliferation assay and the IL-10 assay.

Examples of prior art teachings related for osteoporosis: Nagpal discloses that bone is regarded as the classical target tissue for vitamin D3 and VDR is highly expressed in primary osteoblasts and osteoblast cell lines. (Nagpal, page 1671, left column at bottom. Boehm also states that $1\alpha,25(OH)_2D_3$ binds to its intracellular receptor, the vitamin D receptor (VDR) which results in heterodimer formation with retinoid X receptor (RXR), and enables high-affinity binding to vitamin D responsive element (VDRE) sequences within, and subsequent transcriptional activation of vitamin D target genes such as the bone proteins osteocalcin and osteopontin. (Boehm, page 265, left column.)

The overwhelming conclusion from these peer reviewed articles is that VDR ligands including VDR mimics such as those presently claimed in the instant application bind to VDR and can be used to treat osteoporosis.

The present application enables the treatment of osteoporosis: The present application states that that the compounds of the invention are useful for treating osteoporosis. (Application, ¶0846).) Assay methods used to evaluate the compounds for osteoporosis include: the RXR-VDR heterodimer assay and the OCN (osteocalcin) Promotor Assay as an indicator and marker for osteoporosis. The desired results are an EC_{50} of 325 or less. (*Id.*, ¶0850) Experimental results for representative compounds of the present invention can be found in Table 3 under the column heading OCN Promoter EC_{50} (nM). (*Id.*, ¶832.)

Examples of prior art teachings for scleroderma and seborrheic dermatitis: Cunningham describes treatment of scleroderma with vitamin D analogs and implicates the known role of the vitamin D analogs binding with vitamin D receptor to effect keratinocyte proliferation and differentiation in the treatment of discuses such as scleroderma. Cunningham et al., "Topical Calcipotriene for Morphea/linear Scleroderma", J. of the Am. Acad. of Derm. 1998, 39(2) 211-215 (see page 214, left column.) The reference by Sapadin et al. describes various treatments for scleroderma including compounds which are bind to the vitamin D receptors, i.e.,

vitamin D analogues calcitriol (1α,25-dihydroxyvitaminD_3) and calcipotreine. (Sapadin, "Treatment of Scleroderma", Arch Dermatology, 2002, 138, 99, at 99, 103-104). Sato *et al.*, implicates 1α,25 $(OH)_2D_3$ in the inhibition of differentiation of human keratinocytes in the treatment of sebocytes which are associated with seborrheic dermatitis. (Sato et al., "Epidermal Growth Factor and 1α,25-Dihydroxyvitamin D_3 Suppress Lipogenesis in Hamster Sebacepous Gland Cells", Soc. For Inv. Derm. 2001, 117(4), 965-969.) See page 969, left column.)

In the article by Basak et al. It was noted that seborrhoeic dermatitis (SD) appeared to have a histogenesis similar to that of psoriasis, when localized in the scalp and is clinically and histologically almost indistinguishable from psoriasis. Thus the treatment modalities of these two entities would be similar. (Basak et al., "Comparative Effects of Calcipotriol and Betamethasone 17-Valerate Solution in the Treatment of Seborrhoeic Dermatitis of the Scalp, European Academy of Dermatology and Venereology, 2001, 15, 86-88, see page 86 bottom right to page 87 top left).

The present application enables the treatment of scleroderma and seborrheic dermatitis: As noted above the present application also provides the RXR-VDR heterodimer assay that provides the VDR activity for compounds (*Id.*, 0848); the Keratinocyte Proliferation Assay (*id.*, ¶¶0847, 0853) and the IL-10 Assay (*id.*, ¶0853).

The teachings from the prior art and the present application clearly provide a correlation between the claimed treatment methods and the assays provided in the application.

It is recognized that a skilled medical practitioner can determine an effective dose without undue experimentation. (MPEP 2164.01(c), 2009.) In addition, Lin et al. notes that 1α,25$(OH)_2D_3$ and analogues can be used topically and be effective when used alone or co administered in combination anti-inflammatory steroids. (Lin et al, "The Pleotropic Actions of Vitamin D", BioEssays 2003, 16, 21-28.) (See also Cunningham, at page 212, left column.) The present application also lists potential treatment methods and formulations. (Application, ¶¶0799-0807.) Both of these references describe methods, formulations and evaluations of treatment methods.

Presence or absence of working examples.

The present application provides numerous examples in Tables 3 and 4 of the compounds evaluated in the various assays, including the following: RXR-VDR heterodimer assay, VDR Caco-2, OCN (osteocalcin) Promoter assay, Mouse Hypercalceimia assay, Keratinocte Proliferation assay, and Il-10 assay. As noted above, the references listed above provide a correlation between the in vitro assays and the claimed treatment methods. These therefore provide working examples. (MPEP 2164.02, 2009).

Nature of the invention

The invention relates to methods of treating mammals of specific diseases: osteoporosis, psoriasis, scleroderma, and/or seborrheic dermatitis. It is not incredible or inconceivable that the recited diseases can be treated as incorrectly implied in the Office Action. On the contrary, the articles by Cunningham and Lin both describe treatments using the known VDR ligand, $1\alpha,25(OH)_2D_3$.

State of the prior art

Selected references from the prior art a have been discussed above. From this it should be apparent that at the time filing, scientists in the field have been investigating and testing compounds suitable to use in treating at least osteoporosis, psoriasis, scleroderma, and/or seborrheic dermatitis. Various assays and human trials have also been used to evaluate various compounds and treatment methods as described above. (See, for example, the discussion Cunningham and Lin above.)

Relative skill of those in the art

The educational level and skill of the artisans will be high in their respective fields, including a master's level or PhD level scientist or medical doctor.

Predictability or unpredictability of the art

While it is acknowledged that the chemical and pharmaceutical arts do not necessarily lend themselves to be *absolutely* predicable that is not the standard. Further, the present invention while novel and non-obvious is an extrapolation of known scientific principles. The compounds for use in the treatment methods are acknowledged as novel and non-obvious. Part of the inventive concept lies in their selection as potential drug candidates to treat the recited diseases, which selection is borne out by data presented in the application.

Breadth of the Claims.

The first paragraph of §112, requires that the scope of the claims must bear a reasonable correlation to the scope of the claims. In re Vaeck, 947 F.2d 488, 495 (Fed. Cir. 1991.)

Claims 21-23, and 39-41 recite to a method of treating osteoporosis, psoriasis, scleroderma, and/or seborrheic dermatitis using one or more of the claimed compounds. Clearly the claims are not overly broad; they refer to at most four different diseases. Each of these diseases are thought to be mediated by a vitamin D receptor ligand (or mimic) interacting with the vitamin receptor (VDR) as discussed above. The compounds recited in the claims are supported by a number of examples and data for the representative number of the examples in the RXR-VDR heterodimer assay, VDR Caco-2, OCN (osteocalcin) Promoter assay, Mouse

Hypercalcemia assay, Keratinocte Proliferation assay, and Il-10 assay are listed in Tables 3 and 4.

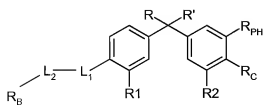
Conclusion:

The overwhelming conclusion from the above analysis is that the present application provides more than sufficient enablement for a skilled artisan to use the claimed invention without using undue experimentation. The prior art and the application itself teach that the novel and non-obvious compounds should be considered to treat the recited diseases i.e., osteoporosis, psoriasis, scleroderma, and/or seborrheic dermatitis. The prior art correlates the data to the recited diseases; and also teach how to further evaluation to compounds for effectiveness. It is well acknowledged that that experimentation is permitted so long as the experimentation in not undue. The application provides a large number of working examples and fully teaches a skilled artisan to perform the assays, prepare formulations, determine appropriate dosages, and routes of application. The level of skill of the artisans is high. The claim breadth is not undue reciting just four diseases, and each is fully supported by the specification and the teaching in the prior art.

The Office Action did not provide a prima facie case for the rejections, and in fact, cannot sustain a rejection for lack of enablement as detailed above. Therefore withdrawal of the rejections of claims 21-23, and 39-41 is requested.

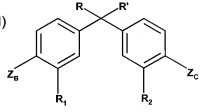
VI. Rejections for Non-Statutory Double Patenting Rejection

Claims 1, 2, 5, 6, 8, 16, 19, 21-23, 26 and 33-31 were rejected under the grounds of provisional non-statutory double patenting over the claims of copending patent application no. 12/470,677 (the "'677 application"). Generic formulae of the compounds claimed in the respective applications are shown below to facilitate the discussion.



The present application

(I)



(I)

The '677 application

The compounds disclosed in the '677 application compounds differ from those claimed notably in the aromatic substituents on the right side. The Z_C group is attached via a carbonyl carbon and include such groups as acids, COOH, esters COOR, (where R is an alkyl), amides, CON, or an alkyl linking groups between the aromatic group and the carbonyl group.

In contrast, the R_c group on the compounds in the instant application are sulfoxides or sulfamides, i.e., the R_c group is attached to the aromatic ring via an oxygen or nitrogen each linking an $-SO_2-$ moiety. Thus the R_c groups are different from the acids, esters, and amides of the Z_c group in the '667 application. The compound claims in the cited reference do not overlap the compound claims in the instant application.

There is no suggestion or teaching proffered that the acids, esters and amides in the '677 application make obvious the sulfoxide or sulfamide substituents in the present application. There is no support or evidence proffered that that the acids, esters and amides in the '677 application are a simple substitution for the sulfoxides or sulfamides, which would yield predictable results; that the use of known techniques were used to improve similar products; that it was obvious to try the modification by choosing between a finite number of identified, predictable solutions; that the modification was known to work in one field of endeavor and led to the variations of the prior art; or that some teaching motivation or suggestion in the prior art to lead a skilled artisan to arrive at the claimed invention. (MPEP §2143, 2009.) In short, there was no reasoning or supporting evidence offered in the Office Action to support the provisional, obviousness-type double patenting rejection.

In light of the above comments, withdrawal of the provisional rejection of claims 1, 2, 5, 6, 8, 19, and 33-38 over the claims in USSN 12/470,677 is requested.

VII. Conclusion

In light of the above claim amendments and comments withdrawal of all rejections is requested. Applicants respectfully request timely reconsideration examination of this application leading to allowance of all elected claims. The Examiner is invited to contact the undersigned attorney by telephone if there are any questions about this Response or other issues that may be resolved in that fashion.

Respectfully submitted,

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